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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,822	02/25/2004	Hon-Wah Man	9516-303	5061

20583 7590 12/02/2005

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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 12/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/786,822	MAN ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,19,21-27,30 and 32-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,19,21-27,30 and 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 5, 19, 21-27, 30 and 32-39 are pending in the application.

This action is in response to applicants' amendment dated September 2, 2005. Claims 1, 5, 19, 21-27, 30 and 32-39 have been amended and claims 20 and 31 have been canceled.

Response to Arguments

Applicant's arguments filed September 2, 2005 have been fully considered with the following effect:

1. With regards to the 35 U.S.C. § 112, first paragraph rejection of claims 25, 26, 36 and 37 labeled paragraph 1 of the last office action, the applicants' arguments have been fully considered, however they were not found persuasive. Applicants argue that the literature references cited throughout the specification suggest that there is a strong correlation between elevated levels of serum TNFα levels in a subject and the occurrence of the progression of various diseases such as cancer, bone resorption diseases, cerebral malaria, referfusion injury, and HIV infection. The applicants' also stated that there are several ways to reduce the serum levels of TNFα, thereby effectively treating such diseases such as via the inhibition of PDE4 and matrix metalloproteinases (MMP). While the specific diseases listed in claims 24 and 35 may be associated with TNFα, PDE4 and matrix metalloprotease (MMP) activity, this does not provide enablement for those diseases and/or disorders listed as well as claimed herein, which is any and all diseases associated with TNFα, PDE4 and matrix metalloprotease (MMP) activity. Treatment of diseases based solely on their efficacious

in inhibiting the activity TNFα, PDE4 and matrix metalloprotease (MMP) activity does not provide for the treatment of every disease and/or disorder claimed herein. Not all diseases and/or disorders are treatable, let alone preventable. There is no evidence that any of the compounds instantly embraced have any one utility generically embraced in claims 25, 26, 36 and 37. Where structure sensitivity exists (in the pharmaceutical art) degree of testing must be representative of claims' scope. Note In re Fisher 166 USPQ 18; In re Surrey 151 USPQ 724. The recent journal article, i.e. Borkakoti (1998), provided herein indicates that several MMP inhibitors currently in clinical trials are being developed as "potential treatment for disease conditions as diverse as cancer therapy, corneal ulceration and arthritis" (page 92).

Another recent journal article, Yu et al. (Sept. 1997) states on page 230 that "there are 3 promising areas in which cancer biology research is likely to have an impact on therapeutics: growth factors and their receptors, matrix metalloproteinases (MMPs) and neoangiogenesis". Yu states that during the past decade the development of synthetic inhibitors targeted at MMPs for the treatment of arthritis, multiple sclerosis and cancer has exploded (page 237, column 2). Yu et al. indicates, "in recent years, various synthetic MMP inhibitors have been shown to restrict tumour growth, and thus inhibit the process of tumour metastasis, in animal models of human diseases" (page 238, column 2). It is also indicated that MMP inhibitor "batimastat is the most extensively studied because of its ability to inhibit primary tumour growth, metastic spread, and secondary tumour growth in vivo", however, in animal studies, "batimastat did not cause any significant reduction in the number of metastases formed from a

primary tumour". MMP inhibitor "BE-16627B, which inhibited tumour cell growth and lung colonisation by human HT1080 fibrosarcoma cells that were overproducing MMP, but did not alter the growth of MMP-deficient human HCT116 colorectal carcinoma cells" (page 239, column 1). Yu et al. concludes "this understanding has led to the identification of MMPs as potential targets for intervention in cancer progression, and the subsequent development of novel MMP inhibitors as a cytostatic approach to cancer therapy".

While Borkakoti indicates that the use of several MMP inhibitors for cancer therapy, corneal ulceration and arthritis are being developed it is speculative in that they may be used in the potential treatment of these disorders. Thus the uses being urged are not in currently available form based on the activity relied on and the specification provides only a starting point for further research. Note Genentech vs. Novo Nordisk 42 USPQ 2d 1001.

Claims 11, 16 and 20-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record and stated above.

2. The applicant's amendments and arguments are sufficient to overcome the 35 USC § 112, second paragraph rejection labeled a), b), d), e), f), h), i), j), k), l), m), o) and p) of the last office action, which are hereby **withdrawn**. However, with regards to the 35 U.S.C. § 112, second paragraph rejections labeled c), g) and n), the applicants'

amendments and remarks have been fully considered but they are not found persuasive.

c) The applicants' state that this item is obviated by the correction of the typographical/clerical errors in claims 1 and 5, however, claim 5 has not been amended with respect to the definition of R^* and R^0, where R^* and R^0 is "imidazolylmethlyl".

g) The applicants' state that this item is obviated by the correction of the typographical/clerical errors in claims 1 and 5, however, claim 5 has not been amended with respect to the definition of R^6 and R^7, where a period appears after the moiety cycloalkoxy of 3 to 6 carbon atoms within the definition of R^6 and R^7.

n) The applicants' state that the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention and to the extent any experimentation is necessary, such experimentation is not undue. Claim 21 is a method of inhibiting the levels of TNFα, claim 22 is a method of inhibiting the levels of matrix metalloproteinases, claim 23 is a method of treating an inflammatory or an autoimmune disease, claim 25 is a method of treating cancer, claim 26 is a method of reducing angiogenesis and claim 27 is a method of inhibiting the levels of phosphodiesterases type IV of which there is no direction to a "specific disease". The applicants also stated that the target diseases are readily identified experimentally, however, only arthritis, rheumatoid arthritis, etc. has been identified with TNFα. The rejection of claims 19-27 and 30-39 was on the

grounds that it is indefinite, in that it is not known which diseases are capable of being responsive to the inhibition of TNFα, PDE4 and matrix metalloprotease (MMP) activity. The scope of diseases and/or disorders associated with the activity of TNFα, PDE4 and matrix metalloprotease (MMP) could alter over time. The applicants' are not entitled to preempt the efforts of others. The applicants also stated that optimization of clinical parameters is routing and that it is well established that these parameters need not be resolved in order to support the claims to methods of treatment where a credible basis for these methods has been established. However, the claims are not directed to a method of treatment but to the method of inhibiting TNFα, PDE4 and matrix metalloprotease (MMP) activity of which it is not known what biological system or physiological effect this pertains, that is the applicants have not set forth the metes and bounds of the claim.

Claims 1, 5, 19, 21-27, 30 and 32-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicant regards as the invention, for reasons of record and stated above.

3. The applicants' amendments are sufficient to overcome the obviousness-type double patenting rejection labeled paragraph 3 in the last office action, which is hereby **withdrawn**.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brenda Coleman

Brenda L. Coleman
Primary Examiner Art Unit 1624
November 23, 2005